CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

CYPERMETHRIN

Chemical Code # 2171, Tolerance # 418
SB 950 # 337

November 3, 1994

I. DATA GAP STATUS

Chronic toxicity, rat:	data gap, inadequate study, no adverse effect indicated
Chronic toxicity, dog:	data gap, inadequate study, no adverse effect indicated
Oncogenicity, rat:	data gap, inadequate study, no adverse effect indicated
Oncogenicity, mouse:	data gap, inadequate study, possible adverse effect indicated
Reproduction, rat:	data gap, inadequate study, possible adverse effect indicated
Teratology, rat:	data gap, inadequate study, no adverse effect indicated
Teratology, rabbit:	data gap, inadequate study, no adverse effect indicated
Gene mutation:	data gap, inadequate study, no adverse effect indicated

Chromosome effects: data gap, inadequate study, no adverse effect indicated

DNA damage: data gap, inadequate study, no adverse effect indicated

Neurotoxicity: not required at this time, possible adverse effect indicated

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Toxicology one-liners are attached.

All record numbers through 124247 and 984941 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T941103
Prepared by Stanton Morris, 11/3/94

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

418-041; 037987; "Cypermethrin: 2 Year Feeding Study in Rats", Report No: CTL/P/669; G.M. Milburn, D. Forbes, P.B. Banham, I.S. Chart, M.J. Godley, C.W. Gore, I. Pratt, M.D.C. Scales, M.D. Stonard, and B.H. Woollen; Imperial Chemical Industries PLC, UK; 6/28/82. Groups of 64 or 128 (0 ppm) Wistar rats/sex were given cypermethrin (batches P19, P24, P26; 88.2 to 93.1% stated purities) in the diet at 0, 20, 150, or 1500 ppm for 104 weeks. At 52 weeks 12 or 24 (0 ppm) rats/sex/group were sacrificed. The high dose was initially 1000 ppm but was raised to 1500 ppm between weeks 3 and 6. Effects seen in both sexes at 1500 ppm were: decreased incidence of distended abdomen, body weight gain, food consumption, red cell volume, plasma cholesterol, plasma triglycerides, urine volumes, and liver, kidney, spleen and heart weights; and increased incidence of hair loss, lymphocyte count, plasma urea, and liver aminopyrine N-demethylase activity and smooth endoplasmic reticulum (NOEL = 150 ppm). No adverse effect was indicated. The study was unacceptable but possibly upgradeable by adequate submissions of analytical data, a rationale for the doses, and individual and summary data for clinical observations (J. Christopher, 8/27/85; S. Morris and J. Gee, 3/17/94)

418-042; 037988: This document contains individual data for the study at DPR doc. # 418-041, rec. # 037987.

418-011; 981937: This document contains a partial duplicate of the study at DPR doc. # 418-041, rec. # 037987.

418-012; 984939: This document contains preliminary data for the study at DPR doc. # 418-041, rec. # 037987.

418-016; 005809: This document contains preliminary data for the study at DPR doc. # 418-041, rec. # 037987.

418-017; 003024: This document contains preliminary data for the study at DPR doc. # 418-041, rec. # 037987.

CHRONIC TOXICITY, RAT

See COMBINED, RAT above.

418-040; 037986; "Toxicity Studies on the Insecticide WL 43467: A Two Year Feeding Study in Rats", TLGR.0189.78; H.E. McAusland, S.T.G. Butterworth, and P.F. Hunt; Shell Toxicology Laboratory (Tunstall); 2-79. Groups of 48 (treated) or 96 (controls) Wistar rats/sex were given dietary mixtures of Cypermethrin (WL 43467, batch 30, 98% stated purity) at 0, 1, 10, 100, or 1000 ppm. Six or 12 (controls) rats/sex/group were sacrificed at 6 and 12 months, 12 or 24 (controls) at 18 months and the remaining 24 or 48 (controls) at 24 months. The only treatment-related effect was decreased group mean body weight and food consumption relative to controls of both sexes at 1000 ppm (NOAEL $\geq$ 1000 ppm). No adverse effect was indicated. The study was unacceptable and not upgradeable because of inadequate analytical method and data, no rationale for the doses used, inadequate serum chemistry data, no urinalysis or ophthalmological performed, and not all individual data (S. Morris and J. Gee, 1/28/94).

CHRONIC TOXICITY, DOG

418-070; 069574; "Cypermethrin: One Year Oral Dosing Study in Dogs", Report No: CTL/P/703; A.E. Kalinowski, P.B. Banham, I.S. Chart, S.K. Cook, C.W. Gore, and S.F. Moreland; Imperial Chemical Industries PLC, Central Toxicology Laboratory, UK; 7/6/82. Cypermethrin (batch P26, 90.6% stated purity, corn oil vehicle) was given daily in gelatin capsules to 6 beagle dogs/sex/group for 52 weeks at 0, 1, 5, or 15 mg/kg/day. Effects seen at 15 mg/kg/day in both

sexes were: transient neurological effects (whole body tremors, gait abnormalities, incoordination, excitability, disorientation, and hypersensitivity to noise), vomiting the first week of treatment, and decreased growth rates. A treatment related increase in liquid feces was seen at 5 and 15 mg/kg/day (NOEL = 1 mg/kg/day). No adverse effect was indicated. The study was unacceptable but possibly upgradeable with adequate submissions of analysis of the test material, individual clinical and ophthalmology data, and an adequate rationale for the doses used (S. Morris and J. Gee, 3/2/94).

418-013; 984940: This document contains a partial duplicate of the study at DPR doc. # 418-070, rec. # 069574.

ONCOGENICITY, RAT

See COMBINED, RAT above.

ONCOGENICITY, MOUSE

418-043; 037989; "Cypermethrin: Lifetime Feeding Study in Mice", Report No: CTL/P/687; S. Lindsay, P.B. Banham, I.S. Chart, D.T. Chalmers, M.J. Godley, and K. Taylor; Imperial Chemical Industries, Central Toxicology Laboratory, UK; 6/23/82. Groups of 60 or 120 (0 ppm) Swiss mice/sex were fed for up to 101 weeks diets containing cypermethrin (3 batches; 91.5, 94.2, 94.0% stated purity) at 0, 100, 400, or 1600 ppm. Ten or 20 (0 ppm) mice/sex/group were sacrificed at 52 weeks. Treatment-related effects at 1600 ppm were decreased body weight gains of both sexes in the first 12 weeks and increased terminal liver weights, decreased interim testes weights, and changes in the distribution of formed blood elements of males (non-oncogenic NOEL = 400 ppm). A **possible adverse effect** was indicated by an increased incidence in benign alveologenic tumors in females at 1600 ppm. The study was unacceptable but possibly upgradeable by adequate submissions of analytical data or certificates of purity

for the test materials (batches P19, ACD/79/134, and 47) and a rationale for the doses used (J. Christopher 8/27/85; S. Morris and J. Gee, 3/9/94).

418-044; 037990: This document contains individual data for the study at DPR doc. # 418-043, rec. # 037989.

418-011; 984938: This document contains a partial duplicate of the study at DPR doc. # 418-043, rec. # 037989.

REPRODUCTION, RAT

418-045; 037991; "Cypermethrin: Three Generation Reproduction Study in the Rat", Report No: CTL/P/683; G.M. Milburn, P.B. Banham, R.D.N. Birtley, M.J. Godley, and S.F. Moreland; ICI Central Toxicology Laboratory, Alderley Park, UK; 7/9/82. Groups of 15 male and 30 female Wistar rats were continuously exposed to diets containing cypermethrin (batches P19, P24, P26; 91.5, 93.1, 90.6% stated purity) at 0, 50, 150, or 750 ppm for 3 generations (F0, F1, F2) with 2 litters/generation (F1a, F1b, F2a, F2b, F3a, F3b). The high dose F0's received 1000 ppm for the first 12 weeks and 750 ppm thereafter. The F0's were first bred at 12 weeks. Ten days after weaning the F1a pups the F0's were bred again to produce the F1b pups. Selected F1b weanlings were exposed for 11 weeks then bred similarly to the F0's to produce the F2a and F2b litters. This cycle was repeated with selected F2b weanlings to produce the F3a and F3b litters. The initial high dose of 1000 ppm produced transient neurological effects between days 3 and 22 in the majority of both sexes of the F0 parents and the death of one male on day 9. Decreased adult body weight gain was seen in F0's in both sexes at 1000 ppm and females at 150 ppm; in F1 females at 750 ppm; and both F2 sexes at 150 and 750 ppm. Adult food consumption was reduced for both F0 sexes at 1000 ppm and F0 females at 150 ppm; and both F1 and F2 sexes at 750 ppm (parental NOEL = 50 ppm). There were no treatment-related effects on reproductive parameters. A **possible adverse effect** was indicated by group mean pup weight gains in the 750 ppm group that were less than controls: for both sexes in all litters at 21, and 28 days $\underline{\text{ποστ παρτυμ}}$ and for both sexes in the F1A, F1B, F2B, and F3B litters at 10 days $\underline{\text{ποστ παρτυμ}}$ (developmental NOEL = 150 ppm). The study was unacceptable but possibly upgradeable with adequate submissions of analytical data for the test material, a rationale for the high dose, compiled gross and histopathology observations, compiled male reproductive and mating performance data, and individual and compiled clinical data for all animals for the entire study (S. Morris and J. Gee, 3/1/94).

418-046; 037992: This document contains individual data for the study at DPR doc. # 418-045, rec. # 037991.

418-013; 984941: This document contains a partial duplicate of the study at DPR doc. # 418-045, rec. # 037991.

418-040; 037985; "Toxicity Studies on the Insecticide WL 43467: A Three Generation Reproduction Study in Rats", TLGR.0188.78; R.W. Hend, R. Hendy and D.J. Flemming; Shell Toxicology Laboratory (Tunstall); 2-79. Groups of 30 Wistar rats/sex were continuously exposed for three generations (F0, F1, F2) with 2 litters/generation to dietary concentrations of cypermethrin (WL 43467, batch 30, 98% stated purity) at 0, 10, 100, or 500 ppm. F0 adults were exposed for 5 weeks before breeding, through two breeding, gestation, and weaning cycles to produce the F1a and F1b litters. F1b pups were exposed for at least 10 weeks then through two breeding, gestation, and weaning cycles to produce the F2a and F2b litters. F2b pups were treated similar to the F1b's to produce the F3a and F3b litters. Post-weaning bodyweight gain and food consumption were reduced at 500 ppm in both sexes and all generations except for the F2 male bodyweight gain and F1 and F2 male food consumption (NOEL = 100 ppm). There were no other treatment-related effects on parental animals, reproductive performance, or pups. No adverse effect was indicated. The study was unacceptable and not upgradeable because there were no analytical data for the test material, no description of the technique used for the diet analysis, no rationale the doses used, inadequate necropsy and histopathology data, and no individual parental data (S. Morris and J. Gee, 1/21/94).

TERATOLOGY, RAT

418-040; 037982; "WL 43467: Effects Upon the Progress and Outcome of Pregnancy in the Rat", LSR Report No. 78/SHL2/364; J.M. Tesh, S.A. Tesh, and W. Davies; Life Science Research, Stock, Essex, England; 10/4/78. Cypermethrin (WL 43467, batch no. 30, 98.2% stated purity, corn oil vehicle) was given by oral gavage to groups of 25 pregnant female Sprague-Dawley CD rats at 0, 17.5, 35, or 70 mg/kg/day on gestation days 6 through 15. The animals were sacrificed on gestation day 21 and the maternal reproductive organs were examined. The fetuses were weighed and examined for external, skeletal, and visceral abnormalities. Maternal effects were seen at 70 mg/kg/day: transient post-dosing neurological disturbances (11/25); convulsions (1/25);

and death (2/25). Bodyweight gain was decreased at 35 and 70 mg/kg/day (maternal NOEL = 17.5 mg/kg/day). There were no treatment related developmental effects (developmental NOEL = 70 mg/kg/day). No adverse effect was indicated. The study was unacceptable but possibly upgradeable with an adequate submissions of analyses of WL 43467 (batch no. 30) and the dosing solutions (S. Morris and J. Gee, 1/14/94).

418-001; 035023:
418-001; 984934:
418-005; 984934: This document contains a brief summary of the study at DPR doc. # 418-040, rec. # 037982 (J. Christopher, 8/27/85).

418-058; 064620: This document contains a brief statement about the study at DPR doc. # 418-040, rec. # 037982.

TERATOLOGY, RABBIT

418-040; 037983; "Toxicity of WL 43467: Teratological Studies in Rabbits Given WL 43467 Orally", Group Research Report TLGR.0010.78; K.M. Dix; Shell Toxicology Laboratory (Tunstall); January, 1978. Cypermethrin (WL 43467, batch no. 30, 98.2% stated purity, corn oil vehicle) was given orally in gelatin capsules to groups of 20 pregnant female banded Dutch rabbits at 0, 3, 10, or 30 mg/kg/day on gestation days 6 through 18. The animals were sacrificed on gestation day 28 and the maternal viscera and reproductive organs were examined. The fetuses were weighed and examined for external, skeletal, and visceral abnormalities. No treatment-related maternal or developmental effect was seen at any dose (maternal and developmental NOEL's $\geq$ 30 mg/kg/day. No adverse effect was indicated. The study was unacceptable but possibly upgradeable with submission of adequate analytical data and rationale for the doses used (S. Morris and J. Gee, 1/18/94).

418-001; 035022:
418-001; 984934:

418-005; 984934: This document contains a brief summary of the study at DPR doc. # 418-040, rec. # 037983 (J. Christopher, 8/27/85).

GENE MUTATION

418-157; 124247; "Salmonella/Mammalian-Microsome Mutagenesis Assay", T1713.501; S. Haworth; Microbiological Associates, Bethesda, MD; 4/2/82. Cypermethrin (FMC 45806, test material identity and purity not stated, DMSO solvent) was tested in a bacterial reverse mutation assay using histidine auxotrophic strains of Σαλμονελλα τψπηιμυριυμ (TA1535, TA1537, TA1538, TA100, and TA98). One trial was conducted with 3 plates/strain/dose being exposed for 48 hours to 0, 100, 500, 2500, 5000, or 10,000 µg/plate with or without metabolic activation (S9 fraction of Aroclor 1254-induced, male Sprague-Dawley rat liver homogenates). The plates were scored for colonies of prototrophic revertants. There was no treatment-related effect on reverse mutation rate. No adverse effect was indicated. The study was unacceptable but possibly upgradeable with submission of adequate identification and statement of purity for the test material (S. Morris and J. Gee, 3/22/94).

418-022; 001841; "An Examination of Cypermethrin for Potential Mutagenicity using the Salmonella/Microsome Reverse Mutation Assay", CTL/P/595; R.W. Trueman; Imperial Chemical Industries Limited, Central Toxicology Laboratory, UK; 11/13/80. Cypermethrin (batch P19, 91.5% stated purity) was tested in a bacterial reverse mutation assay using histidine auxotrophic strains of Salmonella typhimurium (TA1535, TA1537, TA1538, TA100, and TA98). Two trials were conducted with 3 plates/strain/dose being exposed for 72 hours to 0, 4, 20, 100, 500, or 2,500 µg/plate with or without metabolic activation (S9 fraction of Aroclor 1254-induced, Sprague-Dawley rat liver homogenates). The plates were scored for colonies of prototrophic revertants. There was no treatment-related effect on mutation rate. No adverse effect was indicated. The study was unacceptable and not upgradeable because there were no positive controls without activation and no rationale for the doses used (J. Christopher, 8/27/85; one-liner, S. Morris, 3/24/94).

418-022; 001842; "Toxicity Studies with Agricultural Chemicals: Mutagenicity Studies with Ripcord in Microorganisms In Vitro and in the Host-Mediated Assay", TLGR.80.059; T.M. Brooks; Shell Toxicology Laboratory (Tunstall); 6/80. Cypermethrin (WL 43467, >98% stated purity, DMSO vehicle) was tested in microbial mutation assays using histidine auxotrophic strains of Escherichia coli (WP2, WP2 uvrA) and Salmonella typhimurium (TA1535, TA1537, TA1538, TA100, and TA98). In 2 trials, E. coli or S. typhimurium were plated with the test material at 0, 0.2, 2.0, 20, 200, or 2000 ug/plate with (2 or 3 plates/dose) or without (4 or 5 plates/dose) S9 metabolic activation and 48 hours later scored for prototrophic colonies. No adverse effect was indicated. The study was unacceptable and not upgradeable because of inadequate analytical data, no positive control without S9, metabolic activation system was not described, and inadequate protocol description (J. Christopher, 8/27/85; one-liner, S. Morris, 3/24/94).

CHROMOSOME EFFECTS

418-022; 001840; "Toxicity studies with WL 43467: Chromosome studies on bone marrow cells of Chinese hamsters after two daily oral doses of WL 43467", TLGR.0136.77; B.J. Dean; Shell Toxicology Laboratory (Tunstall); 12/77. Groups of 6 Chinese hamsters/sex were dosed by oral gavage with cypermethrin (WL 43467, purity not stated, DMSO vehicle) at 20 or 40 mg/kg/day for 2 days. The animals were treated with Colcemid (0.04% solution, 0.01 ml/g b.w., i.p.) 90 minutes before being killed 8 or 24 days after the last dose and chromosome spreads were prepared from femoral bone marrow. One hundred metaphase cells from each animal were examined for chromosome aberrations. There was no treatment-related effect on chromosome aberrations. No adverse effect was indicated. The study was unacceptable but possibly upgradeable with adequate submissions of analysis of the test material and dosing solutions and an adequate rationale for the doses used (J. Christopher, 8/27/85; one-liner, S. Morris, 3/24/94).

DNA DAMAGE

418-098; 091345; "Cypermethrin: Assessment for the Induction of Unscheduled DNA Synthesis in Rat Hepatocytes", Report No: CTL/P/3080; J.C. Kennelly; ICI Central Toxicology Laboratory, Cheshire, UK; 8/20/90. Cypermethrin (technical, batch number P32, 74.8% stated purity, corn oil vehicle) was given to male Alderley Park rats by oral gavage at 0, 100, or 200 mg/kg. Four or 12 hours later, hepatocytes were isolated and cultured in the presence of ^{3}H-thymidine for 4 hours. Unscheduled DNA synthesis (UDS) was determined by autoradiographic analysis of tritium incorporation into nuclear material. Two trials were run with a total of 5 treated rats/dose/time point. The positive controls were adequate. There was no treatment-related increase in UDS. No adverse effect was indicated. The study was unacceptable and not upgradeable because there were no analysis of the dosing materials, no hepatocyte viability data, and the assay could not detect rapidly-repaired DNA damage (S. Morris and J. Gee, 2/4/94).

418-022; 035025; "Toxicity Studies with Agricultural Chemicals: Mutagenicity Studies with Ripcord in Microorganisms In Vitro and in the Host-Mediated Assay", TLGR.80.059; T.M. Brooks; Shell Toxicology Laboratory (Tunstall); 6/80. Cypermethrin (WL 43467, >98% stated purity, DMSO vehicle) was tested in microbial gene conversion assay using a histidine/tryptophan auxotrophic strain of Saccharomyces cerevisiae (JD1). In 2 trials, samples of liquid suspension cultures of S. cerevisiae were exposed at 0, 0.01, 0.1, 0.5, 1.0, or 5.0 mg/ml for 1 or 4 hours with or 1 hour without S9 metabolic activation. The samples were plated on selection media with 4 plates/dose/time point/loci and 3 days later scored for histidine or tryptophan prototrophic colonies. In 3 trials, 3 mice/dose were dosed by oral gavage with 0, 25, or 50 mg/kg. Immediately after dosing, suspensions of S. cerevisiae were injected ip into each mouse. Five hours later suspensions of S. cerevisiae were harvested and plated on selection media with 4 plates/dose/loci and 3 days later scored for histidine or tryptophan prototrophic colonies. No adverse effect was indicated. The study was unacceptable and not upgradeable because of inadequate analytical data, DMSO vehicle, metabolic activation system was not described, insensitivity of the host mediated assay, and inadequate protocol description (J. Christopher, 8/27/85; one-liner, S. Morris, 3/24/94).

NEUROTOXICITY

418-001; 035024: This document contains a summary of a study in which 10 male rats/dose were fed diets containing 0, 1250, 2500, or 5000 ppm of cypermethrin for 14 days. Clinical signs of neurotoxicity were seen at 1250, 2500, and 5000 ppm. **A possible adverse effect** was indicated by histopathological damage of the sciatic nerve seen in one 5000 ppm animal. The study was unacceptable because it was only a summary (J. Christopher, 8/27/85; one-liner, S. Morris, 3/24/94).

418-040; 037984: "The Acute Oral Toxicity (LD50) and Neurotoxic Effects of Cypermethrin to the Domestic Hen", CTL/C/1077; N.L. Roberts, C. Fairley, D.E. Prentice and L. Cooke; Huntingdon Research Centre, Huntingdon, England; 7/3/81. Technical cypermethrin (batch no P25, 87.8% state purity, nominal cis:trans ratio of 53:47) was given by oral gavage to groups of 10 hens at 0, 2500, 5000, or 10000 mg/kg and observed for 21 days. The hens were then sacrificed and histopathological examinations were done on spinal cord and sciatic nerve. There were no treatment-related effects on body weight, food consumption, ataxia, or histopathology (NOEL and NOAEL $\geq$ 10000 mg/kg). No adverse effect was indicated. The study was unacceptable and not upgradeable because there were no analytical data for the test material and the dosing solutions, no randomization of the hens, inadequate rationale for the doses, sections of medulla oblongata were not taken, and there was no second dose and 21-day observation period (S. Morris and J. Gee, 11/1/94).

These documents have been reviewed:
418-022; 001840
418-022; 001841
418-022; 001842
418-017; 003024
418-016; 005809
418-001; 035022
418-001; 035023
418-001; 035024
418-022; 035025
418-040; 037982
418-040; 037983
418-040; 037984
418-040; 037985
418-040; 037986
418-041; 037987
418-042; 037988
418-043; 037989
418-044; 037990
418-045; 037991
418-046; 037992
418-058; 064620
418-070; 069574
418-098; 091345
418-157; 124247
418-001; 984934
418-005; 984934
418-011; 984937
418-011; 984938
418-012; 984939
418-013; 984940

418-013; 984941

These documents are on the Data Index printout but are not found in the volume:
418-057; 062707

These documents are on the Data Index printout but do not contain data about Cypermethrin:
418-058; 064621
418-074; 067058
418-074; 067059
418-115; 118644
418-134; 118780
418-135; 118781
418-136; 118782
418-137; 118783